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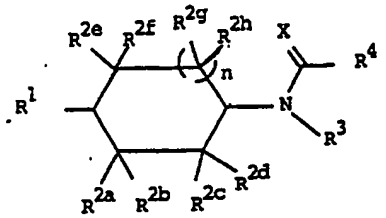
(54) N.N-disubstituierte Arylcycloalkylamine, ihre Salze mit physiologisch verträglichen organischen oder anorganischen Säuren, Verfahren zur Herstellung dieser Verbindungen und diese enthaltende Arzneimittel

(57) Beschrieben werden N.N-disubstituierte Arylcycloalkylamine der allgemeinen Formel I



(I)

mit den in der Beschreibung gegebenen Bedeutungen der Substituenten X, R^1 bis R^4 und von n. Die Verbindungen sind Hemmer der Cholesterinbiosynthese und eignen sich in Arzneimitteln zur Behandlung von Hyperlipidämien und der Atherosklerose.

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Description

The invention relates to N,N-disubstituted arylcycloalkylamines, their salts with physiologically tolerated organic or inorganic acids, processes for the preparation of these compounds and medicaments containing the latter.

The importance of elevated serum cholesterol levels as a major risk factor for the development of atherosclerotic vascular lesions is generally acknowledged. Since most of the cholesterol in the body is self-synthesized and only a small part is taken in with the diet, inhibition of the biosynthesis is a particularly attractive way of lowering elevated cholesterol levels. Since cholesterol biosynthesis proceeds over a large number of stages there are various possibilities for intervention.

Most importance has been achieved by compounds of the mevinolin type, which are already used in therapy. These are substituted 3,5-dihydroxy carboxylic acids or δ-lactones derived therefrom, which are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl(HMG)-CoA reductase, that is to say intervene in an early stage of cholesterol biosynthesis.

Other classes of compounds which intervene in various ways at least in vitro in cholesterol biosynthesis are, for example, the oxysteroids, squalene derivatives and naphthylamine derivatives, such as naftifine and terbinafine. A compilation of these compounds is to be found in J. Amer. Chem. Soc. 111, 1508-10 (1989). Mention should also be made of isoprenoid(phosphinylmethyl)phosphonates which are inhibitors of the enzyme squalene synthetase (J. Med. Chem. 31 (10) 1869-1871 (1988)).

Only a few bioactive 5- to 7-membered N,N-disubstituted arylcycloalkylamines in which one N substituent is the acyl, thioacyl or imidoyl radical are described in the literature.

Il Farmaco, Ed. Sci. 1970, 25, 248-94 (CA 73, 2397r) describes N,N-disubstituted phenylcyclohexylamines with a local anaesthetic and hypertensive effect.

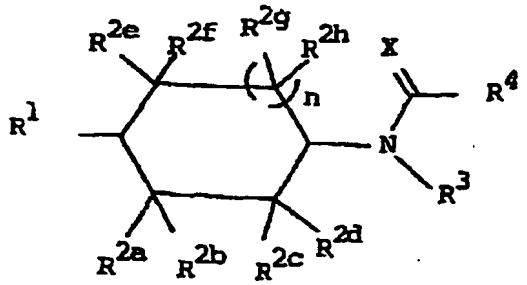
4-Tetrazolylcyclohexylamines with analgesic and antiinflammatory effect are described in Il Farmaco, Ed. Sci. 1984, 39, 1024-37 (CA 102, 197808y).

4-Phenylcyclohexylamines which are ACE inhibitors are to be found in the European application EP 103 927 (CA 101, 91447u), J. Med. Chem. 1983, 26, 1267-77 (CA 99, 88551h) and Drug. Dev. Res. 1986, 26, 141-51 (CA 104, 179906r). 5- to 7-membered arylcycloalkylamines in which one N substituent is the acyl, thioacyl or imidoyl radical and which have an inhibitory effect on cholesterol biosynthesis have not yet been described.

BE patent 772010-Q (31.8.70) claims inter alia substituted 4-arylcyclohexylamines with anticonvulsant, CNS-stimulating and hypotensive effect which, besides other substituents, are substituted on the nitrogen by alkyl radicals having 1 to 4 carbon atoms and alkanoyl radicals having 1 to 3 carbon atoms. However, not a single compound of this structural type is described in this patent.

It has been found, surprisingly, that N,N-disubstituted arylcycloalkylamines in which one N substituent is the acyl, thioacyl or imidoyl radical are very good inhibitors of cholesterol biosynthesis with a mechanism of action which differs from that of HMG-CoA reductase inhibitors.

The N,N-disubstituted arylcycloalkylamines and their salts of the present invention have the general formula I



(I)

In the general formula I:

n is the numbers 0 or 1,

X is the oxygen or sulphur atom or an imino group of the formula $=NR^5$

R^1 is a mono-, di- or trisubstituted phenyl group which may be substituted by 1 to 3 straight-chain or branched alkyl groups having 1 to 4 carbon atoms, by the phenyl group, by 1 or 2 hydroxyl groups, one halogen atom such as, for example, a fluorine or chlorine atom, the benzyloxy, allyloxy or propargyloxy group, by 1 to 3 alkoxy groups having 1 to 4 carbon atoms in the straight-chain or branched alkyl radical, where the alkyl radical in turn may be substituted by an amino group of the general formula $-NR^6R^7$, by a formyl group or an aliphatic acetal group having up to 4 carbon atoms, R^1 is furthermore a furyl, thienyl or pyrimidinyl group which may optionally be substituted by alkyl and/or alkoxy radicals having 1 to 3 carbon atoms, and the pyridyl group and the naphthyl group,

R^{2a} to R^{2h}, which may be identical or different, are a hydrogen atom, an alkyl or alkenyl group having 1 to 3 carbon atoms,

R^3 is a straight-chain or branched alkyl, alkenyl or alkynyl group having 1 to 5 carbon atoms, the phenyl group, the cyclohexyl group and the cyclohexylmethyl group,

R^4 is a straight-chain or branched alkyl or alkenyl group having 3 to 19 carbon atoms, in which the carbon chain may be interrupted by an oxygen or sulphur atom,

and the alkenyl moiety contains 1 to 3 double bonds, a phenylalkyl or phenylalkenyl group having 1 to 4 carbon atoms in the alkylene moiety or 2 to 4 carbon atoms in the alkenylene moiety, where the phenyl moiety may be substituted by an alkyl or alkoxy group having 1 to 3 carbon atoms, or is the phenyl group which may optionally be substituted by 1 or 2 alkyl or alkoxy groups having 1 to 3 carbon atoms or by 1 or 2 halogen atoms such as, for example, fluorine, chlorine or bromine atom, or is the cyclohexyl group or a cyclohexylalkyl or cyclohexylalkenyl group, where the alkylene moiety has 1 to 4 carbon atoms or the alkenylene moiety has 2 to 4 carbon atoms, but R^4 may also be the biphenyl group or a furyl, thienyl or pyridyl group which is optionally substituted by alkyl groups having 1 to 3 carbon atoms,

R^5 is the phenyl group or the p-toluenesulphonyl group,

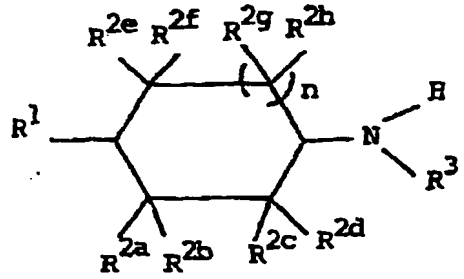
R^6 and R^7, which may be identical or different, are a hydrogen atom, a phenyl group, a straight-chain or branched alkyl group having 1 to 6 carbon atoms which may optionally be substituted by a phenyl radical, it further being possible for

R^6 and R^7 to form, together with the nitrogen atom and, where appropriate, a further oxygen atom, the piperidino, morpholino or pyrrolidino groups.

Preparation methods

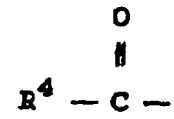
The compounds of the general formula I can be prepared by the following methods:

A) Compounds in which X is an oxygen atom and R^1 to R^4 and n have the aforementioned meanings can be prepared by reacting amines of the general formula II



(II)

in which
R^1, R^{2a} to R^{2h}, R^3 and n have the aforementioned meanings, with an acid derivative of the general formula III



(III)

in which
R^4 has the aforementioned meanings, and Y is a reactive exchangeable group such as, for example, a halogen atom, preferably a chlorine atom, or the imidazolide group.

If Y is a halogen atom, the reactions are carried out in inert solvents such as ether, toluene, methylene chloride and the like, preferably at temperatures between -50°C and 50°C and in the presence of an agent which binds hydrogen halide, such as tertiary amines, sodium carbonate or calcium carbonate. It is moreover possible to employ not only the free amines of the general formula II but also the salts thereof, from which the amines can be liberated in situ by suitable bases, e.g. tertiary organic amines.

If Y is the imidazolide radical, the reactions are preferably carried out in a high-boiling solvent such as xylene at the reflux temperature.

If the radical R^1 comprises sensitive substituents or substituents which interfere with the reaction, such as, for example, the hydroxyl group, the primary or secondary amino group, or the formyl group, it is

advisable for these to be provided with protective groups in a known manner before the reaction, and for these protective groups to be eliminated again after the reaction is complete.

Examples of suitable protective groups are for the hydroxyl group the methyl group, which can be eliminated by boron tribromide or sodium thioethanolate, for the amino group the tert-butoxycarbonyl radical, which can be eliminated with trifluoroacetic acid, and for the formyl radical an acetal group, which can be eliminated with acid.

B) Compounds of the formula I in which X is an oxygen atom, n, R^{2a} to R^{2h}, R^3 and R^4 are defined as at the outset, and R^1 is a phenyl group which is substituted by the benzyloxy, allyloxy, propargyloxy group or by a straight-chain or branched alkoxy group having 1 to 4 carbon atoms, which in turn may be substituted in the alkyl moiety by an amino group of the general formula NR^6R^7 with the meanings indicated above for R^6 and R^7, by an alkoxy group having 1 to 3 carbon atoms, a formyl or acetal group, where the phenyl radical may optionally also contain one or two straight-chain or branched alkyl groups having 1 to 4 carbon atoms and/or a halogen atom, can be obtained by reactions of compounds of the general formula I in which X is an oxygen atom, and n, R^{2a} to R^{2h}, R^3 and R^4 are as defined above, and R^1 is a monohydroxyphenyl radical which may optionally also contain one or two straight-chain or branched alkyl groups having 1 to 4 carbon atoms and/or a halogen atom, with compounds of the general formula IV

R^8-Z (IV)

in which

R^8 is benzyl, allyl or a propargyl group or a straight-

chain or branched alkyl group having 1 to 4 carbon atoms, where the alkyl group in turn may be substituted by an amino group of the general formula $-NR^6R^7$ with the meanings indicated above for R^6 and R^7, by an alkoxy group having 1 to 3 carbon atoms, a formyl group or acetal group, and

Z is a chlorine, bromine or iodine atom or a sulphonyloxy group such as, for example, the p-toluenesulphonyloxy group.

The reaction is carried out in a solvent such as ethanol, tert-butanol, tetrahydrofuran or dimethylformamide at temperatures between 0°C and 100°C in the presence of a base such as potassium carbonate, sodium ethanolate, potassium tert-butanolate or sodium hydride.

If the radical R^8 comprises sensitive substituents or substituents which interfere with the reaction, such as, for example, the primary or secondary amino group or the formyl group, it is advisable for the latter to be provided with protective groups in a known manner before the reaction and for these to be eliminated again after the reaction is complete. Suitable protective groups have already been described hereinbefore.

C) Compounds of the general formula I in which X is an oxygen atom, n, R^{2a} to R^{2h}, R^3 and R^4 are as defined at the outset, and R is the phenyl group which is substituted in position 4 by an alkoxy group having 1 to 4 carbon atoms, which in turn contains an amino group of the formula $-NR^6R^7$, where the phenyl radical may optionally also contain one or two straight-chain or branched alkyl groups having 1 to 4 carbon atoms and/or a halogen atom, can be obtained by reacting a compound of the general formula I in which X, n, R^2 to R^4 are as defined above and R^1 is a phenyl group which [lacuna] in position 4 by an alkoxy group having 1 to 3 carbon atoms which in turn is substituted by a formyl

group, where the phenyl radical may optionally also contain one or two straight-chain or branched alkyl groups having 1 to 4 carbon atoms and/or a halogen atom, with an amine of the general formula V

HNR^6R^7 (V)

in which R^6 and R^7 are defined as mentioned at the outset, or with salts thereof with inorganic or organic acids in the presence of reducing agents. Suitable reducing agents are sodium cyanoborohydride or catalytically excited hydrogen.

These reactions are carried out in solvents such as alcohols, tetrahydrofuran, dioxane, water or mixtures of these solvents at temperatures between 0 and 100°C, preferably at room temperature.

In cases where the radical $-NR^6R^7$ is a primary amino group, the process can be modified in such a way that the Schiff's base produced as intermediate is isolated and reacted with reducing agents such as sodium boronate or catalytically excited hydrogen.

D) The compounds of the general formula I in which X is an oxygen atom, and n and R^1 to R^4 are as defined at the outset, can be obtained by reacting compounds of the formula I in which n and R^1 to R^4 are as defined at the outset, and X is an oxygen atom, with sulphur reagents such as diphosphorus pentasulphide or Lawesson's reagent.

The reactions can be carried out in inert solvents such as acetonitrile, toluene or xylene at temperatures between 0 and 150°C. A review of reactions with Lawesson's reagent is to be found in Tetrahedron Letters 41, 2567 (1985).

If the constituent R^1 comprises sensitive substituents

or substituents which interfere with the reaction, such as, for example, the hydroxyl group, a primary or secondary amino group or the formyl group, it is advisable for the latter to be provided with protective groups in a known manner before the reaction and for these protective groups to be eliminated again after the reaction is complete.

Examples of suitable protective groups are for the hydroxyl group the methyl group, which can be eliminated by boron tribromide or sodium thioethanolate, for the amino group the tert-butoxycarbonyl radical, which can be eliminated with trifluoroacetic acid, and for the formyl radical an acetal group, which can be eliminated with acid.

E) Compounds of the general formula I in which X is the group $=NR^5$ in which R^5 is the phenyl group, and R^1 to R^4 and n are as defined at the outset, can be prepared by initially converting compounds of the general formula I in which X is an oxygen atom, and n and R^1 to R^4 are as defined at the outset, with acid chlorides such as thionyl chloride, phosphorus oxychloride, phosgene or oxalyl chloride or with alkylating agents such as dimethyl sulphate, into reactive derivatives which are then reacted with aniline.

The reactions can be carried out in inert solvents such as ether, methylene chloride, chloroform or toluene at temperatures between -40°C and the boiling point of the particular solvent.

If the substituent R^1 comprises sensitive substituents or substituents which interfere with the reaction, such as, for example, the hydroxyl group, a primary or secondary amino group, or the formyl group, it is advisable for these to be provided with protective groups in a known manner before the reaction and for these protective groups to be eliminated again after

the reaction is complete.

Examples of suitable protective groups are for the hydroxyl group the methyl group, which can be eliminated by boron tribromide or sodium thioethanolate, for the amino group the tert-butoxycarbonyl radical, which can be eliminated with trifluoroacetic acid, and for the formyl radical an acetal group, which can be eliminated with acid.

F) Compounds of the general formula I in which X is the group $=NR^5$ in which R^5 is the p-toluenesulphonyl group, and R^1 to R^4 and n are as defined at the outset, can be prepared by reacting compounds of the general formula I in which X is an oxygen atom, and R^1 to R^4 and n are as defined at the outset, with p-toluenesulphonyl isocyanate, preferably in boiling toluene.

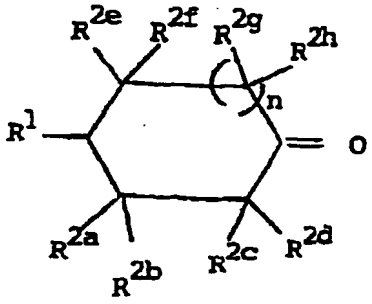
If the substituent R^1 comprises sensitive substituents or substituents which interfere with the reaction, such as, for example, the hydroxyl group, a primary or secondary amino group, or the formyl group, it is advisable for these to be provided with protective groups in a known manner before the reaction and for these protective groups to be eliminated again after the reaction is complete as already described above.

The compounds of the general formula I prepared by the above processes can be purified and isolated by known methods, e.g. crystallization, distillation or chromatography. They may if desired, if basic radicals are present, be converted into their salts with organic or inorganic acids by methods known per se.

The radicals R^1 and R^2, and the nitrogen atom, in the compounds of the formula I according to the invention may assume either the equatorial or the axial disposition. The invention encompasses both the pure isomeric forms and mixtures of the various isomers.

Starting materials

The starting compounds of the general formula II can be obtained from ketones of the general formula VII



(VII)

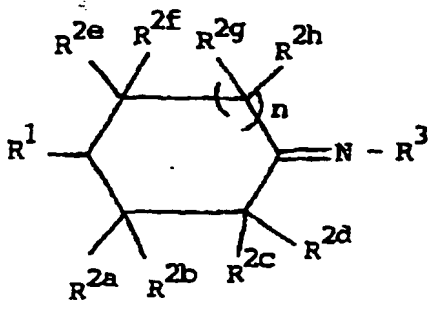
in which

n, R^1 and R^{2a} to R^{2h} are as defined at the outset, and amines of the general formula VIII

H_2NR^3 (VIII)

in which

R^3 is as defined at the outset, in the presence of reducing agents. The reaction can moreover be managed in such a way that either the reaction mixture is converted directly into compounds of the formula II, e.g. in the presence of sodium cyanoborohydride or catalytically excited hydrogen, or that initially the Schiff's base of the formula IX

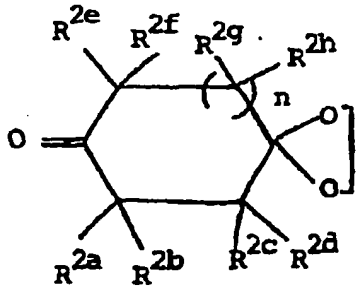


(IX)

which results as intermediate is isolated and then reduced, e.g. with sodium boranate or catalytically excited hydrogen.

The ketones of the formula VII can be prepared by known methods, e.g. from monoethylene ketals of the general

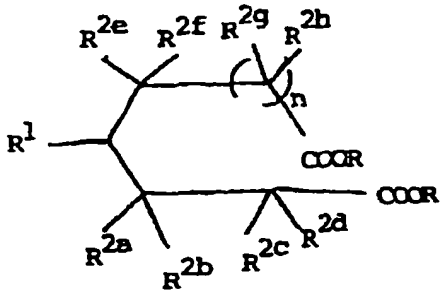
formula X



(X)

and an organometallic compound R^1-Me where R^1 is as defined at the outset, and Me is a lithium atom or the group Mg Hal in which Hal is a halogen atom, preferably a chlorine atom, followed by elimination of water, hydrogenation of the resulting double bond and hydrolysis of the ketal group. The process can be modified in such a way that, if required, one or more substituents R^2 are introduced after the end of the reaction sequence, e.g. by alkylation of the ketone enolate ion.

A further preparation method is Dieckmann cyclization of diesters of the general formula XI



(XI)

and subsequent hydrolysis and decarboxylation by methods known per se. R in the general formula XI is any alkyl, aralkyl or aryl radical.

The compounds of the general formula I have interesting biological properties. They are inhibitors of cholesterol biosynthesis.

Because of their biological properties, they are particularly suitable for the treatment of hyperlipidaemias, in particular of hypercholesterolaemia,

hyperlipoproteinaemia, hypertriglyceridaemia and the atherosclerotic vascular lesions resulting therefrom, with their sequelae such as coronary heart disease, cerebral ischaemia, intermittent claudication and others.

The biological effect of compounds of the formula I was determined by measuring the inhibition of ^{14}C-acetate incorporation into steroids which can be precipitated with digitonin, by the following method:

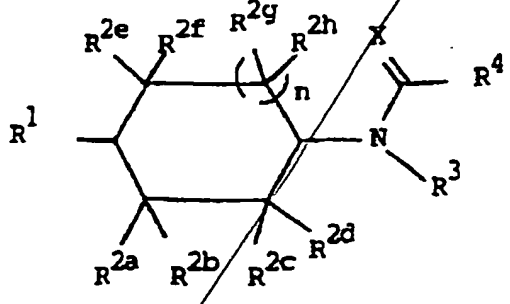
Method

Human hepatoma cells (Hep G2) are cultured for 3 days and then stimulated for 16 hours in cholesterol-free medium. The substances to be tested (dissolved in dimethyl sulphoxide; final concentration 0.1%) are added during this stimulation period. After addition of 200 µmol/l 2-^{14}C-acetate, incubation is continued in an incubator at 37°C for a further 2 hours.

After detachment of the cells and hydrolysis of the cholesterol ester, cholesterol is extracted and precipitated with digitonin. The ^{14}C-acetate incorporated into cholesterol is determined by scintillation measurement.

Patent claims

1. N,N-Disubstituted arylcycloalkylamines of the general formula I



(I)

in which